REMARKS

Applicants and the undersigned wish to thank Examiner Sheridan Swope, Ph.D. for the courtesy of her time to discuss and reconsider the finality status of the office action on February 26, 2007. Additionally, Applicants thank Examiner for withdrawing the final office action dated January 19, 2007 and replacing it with the non-final office action dated March 6, 2007, to which Applicants respond herein.

In the office action dated March 6, 2007, the Examiner withdrew the objections to the specification and claims, maintained the obviousness-type double patenting rejection, maintained the enablement and written description rejections, maintained the anticipation rejections, and maintained the obviousness rejections. Applicants address each of the maintained rejections below.

In view of the amendments noted above and the remarks below, Applicants respectfully request the merits of this patent application be reconsidered.

No extension of time is believed to be necessary and no fee is believed to be due in connection with this response. However, if any extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. No other fee is believed to be due in connection with this response. However, if any fee is due in this or any subsequent response, please charge the fee to the same Deposit Account No. 17-0055.

Status of the Claims

Claims 1, 7-11, 15, 17, 37, 39, and 41-45 are pending in this matter. Claims 1, 7, 17, 37, 39, 41, and 42 are currently amended. Claim 45 is new. Support for claim 45 can be found in the application as filed. No new matter has been added.

Claim rejections under 35 U.S.C. §101

The Examiner maintained the rejection against claims 1, 7-11, 15, 17, and 37-44 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-13, 19-22, and 24-28 of U.S. Application No. 10/986,695. Applicants believe that the rejection is still a provisional rejection because U.S. Application No. 10/986,695 is still pending (see MPEP § 804II.B. ¶8.34 Examiner Note:2 and ¶8.35). Applicants stand ready to address the rejection should it be maintained as an actual rejection in the future if U.S. Application No. 10/986,695 issues at a future time at which the present application remains pending. If the present application issues first, the obviousness-type double patenting rejection will become moot.

Enablement rejection under 35 U.S.C. §112-first paragraph

The Examiner has maintained the rejection of claims 1, 7-11, 15, 17, and 37-44 for failing to meet the enablement requirement, alleging that the specification does not enable all methods of treating cerebral vascular disease using any compound that decreases the activity of any CYP4A or CYP4F 20-HETE synthesizing enzyme. In particular, the Examiner alleged that the specification fails to support reasons (A)-(G) of the office action. Applicants traverse the rejection below.

With regard to reason (A) on page 4 of the office action, Applicants submit that the rejection with regard to reason (A) has been overcome by amending the claims. Specifically, claim 1 has been amended to recite the use of a known inhibitor of a CYP4A or CYP4F enzyme. By definition, one of skill in the art is familiar with known inhibitors by their structure and function and therefore can readily use them to practice the present invention. For example, it is known in the art that DDMS is an inhibitor of CYP4A1 and CYP4A3 (Wang et al. 1998, page 971, paragraph 2) and the present application has shown that HET0016 is an inhibitor of CYP4A11, CYP4F2, and CYP4F3. Accordingly, Applicants submit that one of skill in the art would possess sufficient guidance to make and use any known inhibitors of a CYP4A or CYP4F enzyme.

With regard to reason (B) bridging pages 4 and 5 of the office action, Applicants note with thanks the Examiner's agreement that identifying new 20-HETE synthesizing enzyme inhibitors is not part of the present invention. Therefore, as amended, Applicants submit that claims 1, 7-11, 15, 17, 37, 39, and 41-44 are enabled for using a known inhibitor of a CYP4A or CYP4F enzyme.

With regard to reason (C) on page 5 of the office action, Applicants note that the claims as amended are now limited to the use of a known inhibitor of a CYP4A or CYP4F enzyme.

With regard to reason (D) on page 5 of the office action, Applicants note that the claims as amended are now limited to the use of a known inhibitor of a CYP4A or CYP4F enzyme.

With regard to reason (E) on page 5 of the office action, Applicants note with thanks the Examiner's agreement that compounds that inhibit CYP4A and/or CYP4F can be used in the recited method.

With regard to reason (F) on page 5 of the office action, Applicants note with thanks the Examiner's agreement that clinical data are not required to enable the invention. Applicants therefore submit that the claims, as amended to recite the use of a known inhibitor of a CYP4A or CYP4F enzyme, are enabled.

With regard to reason (G) on page 5 of the office action, Applicants note with thanks that the Examiner withdrew her argument with respect to Hoagland et al.

Accordingly, as Examiner's reasons (A) through (G) have been appropriately addressed by the claims amendments, Applicants respectfully submit that the rejection of claims 1, 7-11, 15, 17, and 37-44 for failing to meet the enablement requirement has been overcome. Withdrawal of this rejection is respectfully requested.

Additionally, claims 7-11, 15, 17, 37, 39, and 44 as amended and new claim 45 recite specific known 20-HETE synthesizing enzyme inhibitors. Claim 7-11 and 44 are limited to the use of HET0016. Claims 15, 17, 37, and 39 as amended and new claim 45 recite the use of HET0016, 17-ODYA, dibromododecenyl methylsulfimide, 1-aminobenzotriazole and miconazole. Therefore, Applicants respectfully submit that claims 7-11, 15, 17, 37, 39, 44, and 45 are enabled also for the recitation of specific inhibitors.

Written description rejection under 35 U.S.C. §112-first paragraph

The Examiner rejected claims 1, 7-11, 15, 17, and 37-44 for failing to satisfy the written description requirement, alleging that the specification does not reasonably describe the genus of all methods of treating the recited cerebral vascular diseases using any compound that decreases the activity of any CYP4A or CYP4F 20-HETE synthesizing enzyme. Applicants traverse the rejection below.

Applicants submit that, as amended, the claims now recite the use of a known inhibitor of a CYP4A or CYP4F enzyme for use with four particular cerebral vascular diseases associated with an increase in the 20-HETE level (*see e.g.*, Example 1 in the application). Applicants submit that the application as filed shows how, using HET0016 and 17-ODYA as examples, inhibiting 20-HETE synthesis using known inhibitors is effective in treating these diseases (*see* Examples 1 and 2 in the application). By definition, one of ordinary skill in the art is familiar with known inhibitors by their structure and function. Therefore, Applicants submit that the written description requirement for the use of a known inhibitor of a CYP4A or CYP4F enzyme is met.

Additionally, claims 7-11, 15, 17, 37, 39, and 44 as amended and new claim 45 recite specific known 20-HETE synthesizing enzyme inhibitors. Claim 7-11 and 44 are limited to the use of HET0016. Claims 15, 17, 37, and 39 as amended and new claim 45 recite the use of HET0016, 17-ODYA, dibromododecenyl methylsulfimide, 1-aminobenzotriazole and miconazole. Therefore, Applicants respectfully submit that claims 7-11, 15, 17, 37, 39, 44, and 45 meet the written description requirement also for the recitation of specific inhibitors.

Claim rejections under 35 U.S.C. §102

1. Alonso-Galicia et al. 1999

The Examiner has maintained the previous rejections of claims 1, 17, 37, 39 and 41 as being anticipated by Alonso-Galicia et al. 1999 (Alonso-Galicia) as evidenced by Wang et al. 1998 (Wang). The Examiner alleges that Alonso-Galicia teaches that intra-cerebroventricular injection of dibromododecenyl methylsulfimide (DDMS) reduces cerebral blood flow (Fig. 7) and that Wang teaches that DDMS inhibits CYP4A1 and CYP4A3. Applicants traverse the rejection below.

As noted by the Examiner in the office action and pointed out by Applicants in the previous response, Alonso-Galicia teaches that intra-cerebroventricular injection of DDMS reduces "cerebral blood flow increase" (caused by the short acting NO donor MAHMA nonoate). However, the claims at issue recite the use of a 20-HETE synthesizing enzyme inhibitor to increase or prevent a decrease in cerebral blood flow. This is not disclosed by Alonso-Galicia.

In response to this argument, the Examiner argues that Alonso-Galicia teaches intra-cerebroventricular injection of the HETE synthesizing inhibitor DDMS and that "the purpose of said injection is irrelevant; it is only necessary for the prior art to teach the same method." The Examiner goes on to state that the "effect of the method is inherent to the method itself." (Office action page 7). Applicant respectfully point out that the Examiner asked the wrong question under *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005) in making the inherency rejection.

Perricone presents a parallel fact pattern to the present application. In *Perricone*, the Federal Circuit was presented with the question of whether a claim (claim 1 in U.S. patent 5,574,063 (the `063 patent)) is anticipated under the doctrine of inherency by a single prior art reference, (U.S. patent 4,981,846 (the `846 patent)). Claim 1 of the `063 patent is directed to a method for treating skin sunburn comprising topically applying to the sunburn a composition. The active ingredients of that composition have been disclosed in the `846 patent in connection with skin cream compositions. Therefore, claim 1 was alleged to be invalid because skin sunburn would be inherently treated by the prior art skin creams. However, the Federal Circuit held that the claim is not anticipated by the `846 patent. The court held that the correct inquiry is not whether the prior art cream, if applied to skin sunburn, would inherently treat the damage, but whether the prior art reference discloses applying the skin cream to sunburn. It does not.

Similarly, for the present application, the correct question to ask is not whether an intra-cerebroventricular injection of the 20-HETE synthesizing inhibitor, if administered to someone who has a cerebral vascular disease, would inherently treat the disease or condition, but whether the prior art reference disclosed administering 20-HETE synthesizing inhibitor to a human or non-human animal who has a cerebral vascular disease to increase or prevent a decrease in cerebral blood flow. Such a disclosure has not been made by Alonso-Galicia. It is noted that claim 1 has been amended to clarify that the

inhibitor is administered to a human or non-human animal having said disease. Therefore, the claims as amended are not inherently anticipated by Alonso-Galicia.

In fact, far from anticipating these claims, Alonso-Galicia actually teaches away from the subject matter of the present claims. Alonso-Galicia teaches using DDMS to reduce blood flow increase; not to increase or prevent a decrease in blood flow as recited in the present claims. Therefore, a skilled artisan would not have administered DDMS to a patient who has the four cerebral vascular diseases recited in claim 1.

2. Su et al. 1999

The Examiner has also maintained the rejection of claims 1, 37, 39, and 41 as being anticipated by Su et al. 1999 (Su) as evidenced by Fotherby et al. 1997 (Fotherby) or Schmidt et al. 2000 (Schmidt). The Examiner alleges that Su teaches that 1-aminobenzotriazole inhibits 20-HETE synthesis (Fig. 1), reduces blood pressure (Fig. 9), and decreases the expression of the HETE synthesizing enzyme CYP4A1. The Examiner goes on to state that Fotherby and Schmidt demonstrate that it is well known in the art that reducing blood pressure is an effective way for treating cerebral vascular diseases. Applicants traverse the rejection below.

As pointed out by Applicants in the previous response, Su teaches that 1-aminobenzotriazole is a 20-HETE inhibitor and lowers blood pressure in spontaneously hypertensive rats (SHR). However, Su does not disclose that 20-HETE inhibitors can lower blood pressure in normotensive rats. In fact, subsequent studies with normotensive rats have shown that 1-aminobenzotriazole caused hypertension when the rats were fed high salt diet and lowered blood pressure when the rats were fed low salt diet. In the same normotensive rats, HET0016 either caused hypertension or did not change the blood pressure (Hoagland et al., Hypertension 42:669-673, 2003).

Furthermore, lowering blood pressure is not an effective treatment for occlusive stroke and hemorrhagic stroke. Fotherby and Schmidt teach that chronic hypertension increases the risk for stroke by promoting arteriolosclerosis and narrowing the cerebral arteries. However, they do not establish that lowering blood pressure is an effective treatment for stroke. Fotherby notes that "[t]he risks and benefits of antihypertensive therapy in the large number of older and frailer stroke patients commonly seen in our hospital remain largely unresolved" (page 625, right column, lines 9-12). Schmidt only mentions that hypertension is associated with stroke but do not provide that lowering blood pressure is an effective treatment. In fact, lowering blood pressure with systemic vasodilators or antihypertensive drugs are counterindicated in the treatment of both occlusive and hemorrhagic stroke.

In response to these arguments, the Examiner argues that Su teaches treatment with a 20-HETE inhibitor and that "the purpose of said treatment is irrelevant; it is only necessary for the prior art to teach

the same method." The Examiner goes on to state that the "effect of the method is inherent to the method itself" (Office action page 7).

Applicant respectfully point out that the Examiner asked the wrong question under *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005) in making the inherency rejection.

As discussed above, according to the court's holding in *Perricone*, the correct inquiry is not whether the treatment disclosed in Su, if applied to a human or non-human animal having a cerebral vascular disease would inherently treat the disease, but whether Su discloses administering a known 20-HETE synthesizing inhibitor to a human or non-human animal having a cerebral vascular disease to increase or prevent a decrease in cerebral blood flow. Such a disclosure has not been made by Su. Therefore, the claims at issue are not inherently anticipated by Su.

For the above reasons, Su, together with Fotherby and Schmidt, do not inherently anticipate the claims at issue.

Claim rejections under 35 U.S.C. §103

1. Roman et al. 1999 (WO 99/43310) in view of Frisbee et al. 2000

The Examiner has maintained the rejection of claims 1, 15, 37, and 39-41 as being obvious over Roman et al. 1999 (WO 99/43310) (Roman) in view of Frisbee et al. 2000 (Fribsee). The Examiner maintains that Roman discloses that cerebral vascular diseases can be treated by blocking the effects of 20-HETE. While the Examiner concedes that Roman does not teach the use of a 20-HETE synthesis inhibitor, the Examiner maintains that Frisbee does, and that it would have been obvious to one of skill in the art to modify the teachings of Roman to use the 20-HETE synthesis inhibitor of Frisbee. Applicants respectfully disagree.

Roman discloses the use of 20-HETE antagonists to treat cerebral vascular diseases (page 5, line 4). 20-HETE antagonists block the 20-HETE receptor while 20-HETE synthesizing enzyme inhibitors inhibit the synthesis of 20-HETE. Nothing in Roman and Frisbee teaches or suggests that replacing the 20-HETE antagonist of Roman with 20-HETE synthesis inhibitors would be feasible, let alone successful.

As shown in the present application, hemorrhagic stroke is associated with an elevation in the formation of 20-HETE in the cerebral circulation and that a 20-HETE synthesizing enzyme inhibitor could be given to treat the acute fall in cerebral blood flow and the vasospasm caused by hemorrhagic stroke. The same is true for occlusive stroke. The levels of 20-HETE in the brain can increase because of increased synthesis or the release of preformed 20-HETE stored in membrane phospholipid pools in (i) blood elements such as white blood cells and platelets, (ii) neural tissues such as brain neurons, (iii) vascular tissues such as vascular myocytes, and (iv) circulates bound to plasma proteins. While a 20-HETE antagonist is effective regardless of what causes the increase in 20-HETE level because it blocks

the downstream 20-HETE receptor, a 20-HETE synthesis inhibitor will not be effective if 20-HETE is released from storage pools. Neither Roman nor Frisbee disclose or suggest that the increase in 20-HETE level in hemorrhagic or occlusive stroke is caused by increased 20-HETE synthesis instead of release from storage pools.

Further, 20-HETE is not the only potential mechanism that could cause reduced blood flow in the four cerebral vascular diseases. There are many other ways that may be the underlining mechanisms that could have caused a reduced cerebral blood flow in the four disease conditions recited in the claims. Without knowing whether there is an increase in 20-HETE synthesis, it is difficult to predict whether known 20-HETE synthesis inhibitors would work. Before the inventors made the present invention, it wasn't known in the art the 20-HETE levels are increased in the four vascular diseases cited in the present claims. Accordingly, Applicants respectfully submit that the Examiner is improperly using hindsight to reconstruct the present claims.

The Examiner argues, citing Harder et al.,1994 (Harder), that it is known in the art that cerebral microvessels produce 20-HETE and that a 20-HETE synthesizing enzyme inhibitor reduces levels of 20-HETE and increases the activity of the k+ channel, suggesting that "more likely than not, other effects of 20-HETE would be inhibited by a 20-HETE synthesis inhibitor. Harder describes *in vitro* studies using blood vessels or cells isolated from animals. Such an *in vitro* system simply lacks the systemic components involved in physiological or disease regulation, principally those of the nervous and endocrine systems. It is well known in the art that these studies have limitations in that physiological conditions and disease conditions are a whole body phenomenon and are regulated and affected by complicated mechanisms and *in vitro* studies simply do not reflect the complexity such as regulation by hormones and so on. Cerebral vascular blood flow is no exception. The art recognizes that there are many differences between cultured cells and their *in vivo* counterparts for a variety of reasons and this has often led to tissue culture being regarded in a rather skeptical light. Therefore, a skilled artisan would not conclude with reasonable certainty that an *in vitro* result would hold true *in vivo*.

Furthermore, Harder did not disclose or suggest that the increase in 20-HETE level in hemorrhagic or occlusive stroke is caused by increased 20-HETE synthesis instead of release from storage pools. Therefore, Harder did not cure the deficiency of Roman and Frisbee. Again, if the four cerebral vascular diseases recited in the present claims are caused by the release of pre-formed 20-HETE stored in membrane phospholipid pools, 20-HETE synthesis inhibitors will not be successful treatments for said diseases. At most, the present invention might be merely obvious to try, but without reasonable likelihood of success.

Accordingly, Applicants submit that the claims at issue are not obvious over Roman in view of Frisbee.

2. Roman et al. in view of Powell et al or Lasker et al.

The Examiner has also maintained the rejections of claims 1, 15, and 37-43 as being obvious over Roman in view of Powell et al. 1998 (Powell) or Lasker et al. 2000 (Lasker). In reply to the arguments presented by the Applicants in the previous response, the Examiner refers to the reasons set forth in the above obviousness rejection over Roman in view of Frisbee. Applicants have responded accordingly above and herein incorporate the arguments by reference. In view of the arguments provided above, withdrawal of this obviousness rejection is respectfully requested.

Summary

Having addressed each issue raised by the Examiner, claims 1, 7-11, 15, 17, 37, 39, and 41-45 as amended are believed to be in condition for allowance and a Notice of Allowance is respectfully requested. Should any issues remain outstanding, the Examiner is invited to contact the undersigned at the telephone number appearing below if such would advance the prosecution of this application.

Respectfully submitted,

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